

# An Analysis of Spontaneous Reports on Adverse Reactions in Child and Adolescents Psychiatry in Germany

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## Background

The use of medicines in child and adolescent psychiatry is increasing and, as a result, a higher number of adverse drug reactions (ADRs) can be assumed. Besides vaccines, methylphenidate and atomoxetine induce the highest number of ADR reports in children [1] and off-label use of antipsychotics and antidepressants in this age group may cause safety problems.

## Aim

To identify potential safety signals for medicines used for psychiatric indications in children and adolescents.

## Methods

Included were reports from the DCGMA database of individual case safety reports (Figure 1) involving antipsychotics, antidepressants or stimulants as suspected medicines and referring to children and adolescents. Besides a descriptive analysis we screened for signals by identifying reactions with  $\geq 3$  reports that are not labeled in the corresponding product information. These potential signals were matched with published reports in PubMed and VigilLyze® [2] (Figure 2).

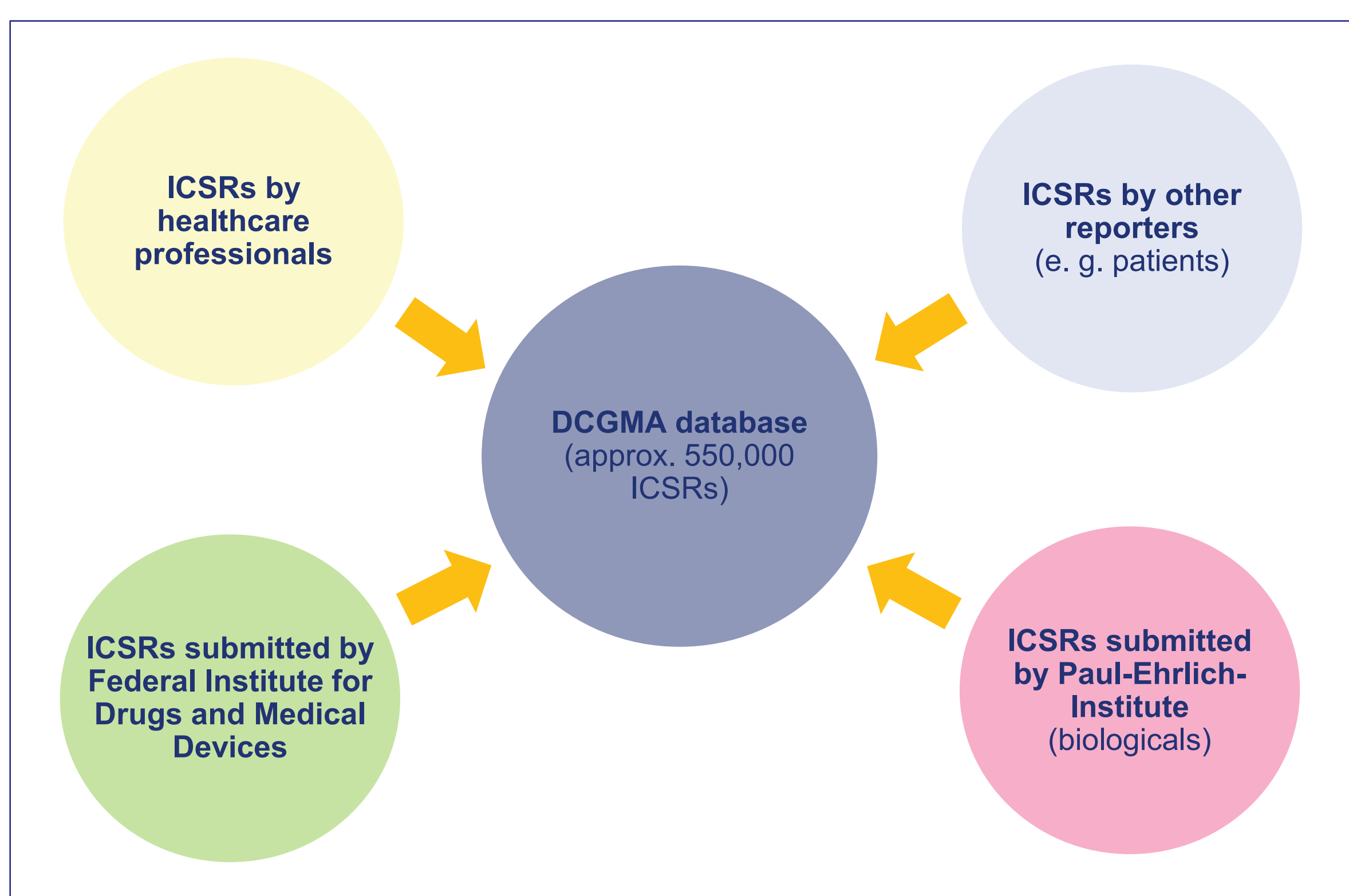


Figure 1: Composition of the database of individual case safety reports of the Drug Commission of the German Medical Association.

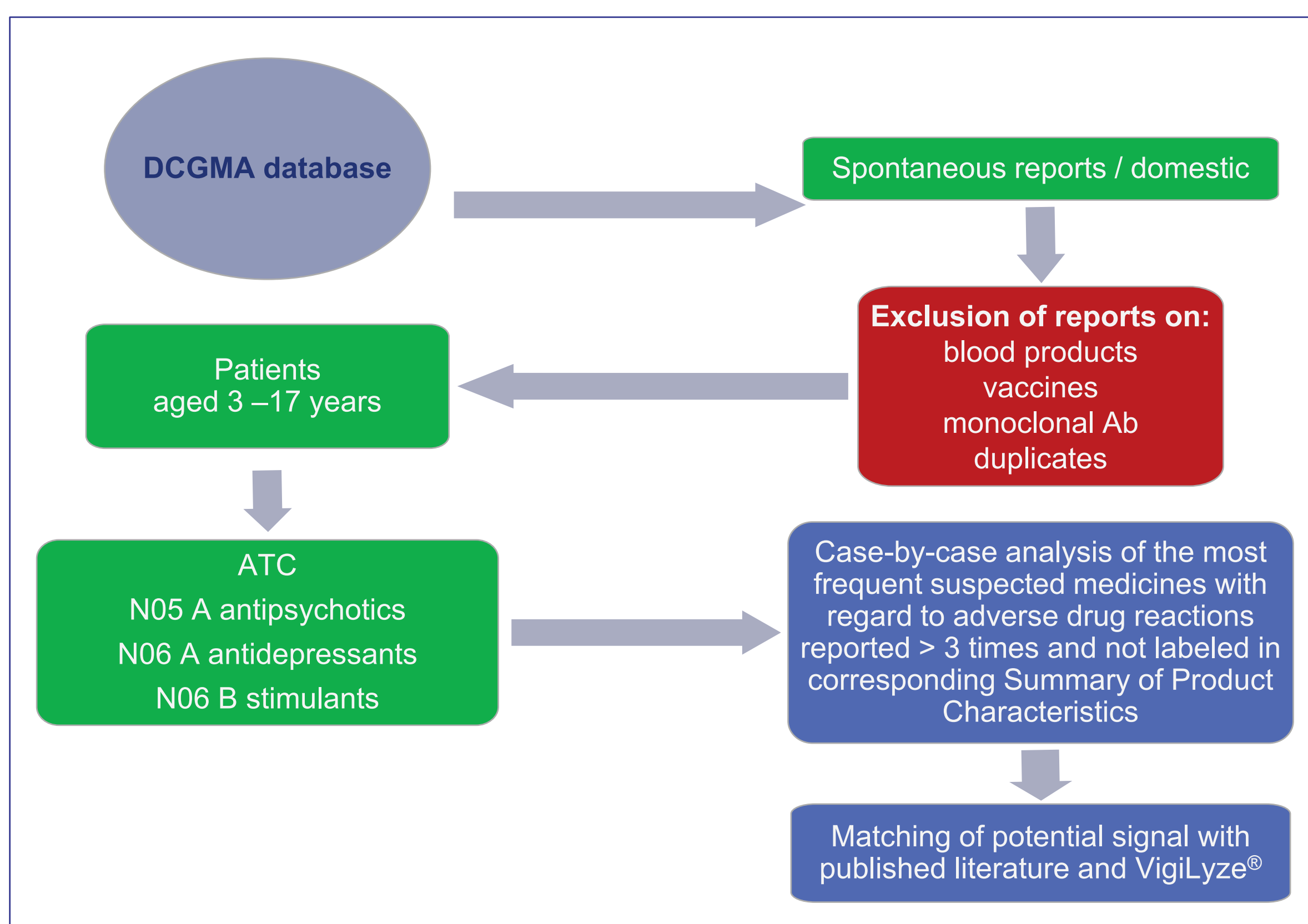


Figure 2: Selection of ICSRs and identification of potential safety signals.

## Results

In approximately 13,400 (4.2 %) of 320,000 reports (1990 to August 2016) referring to small molecule drugs, the affected patients were between the ages of 3 to 17. The proportion of reports with suspected psychoactive medicines in this age group was about 20 % and has increased since the late 1990s. Most frequently suspected were stimulants (41 %), followed by antipsychotics (36 %), and antidepressants (23 %). Among the three most frequently suspected substances in each group citalopram and venlafaxine are not approved for this age group and risperidone and aripiprazole are known to be also prescribed off-label pertaining to indication [3]. Potential signals were identified for the substance with the highest total number of reports, methylphenidate ( $n = 930$ ) and for lisdexamfetamine ( $n = 92$ ) (Table 1).

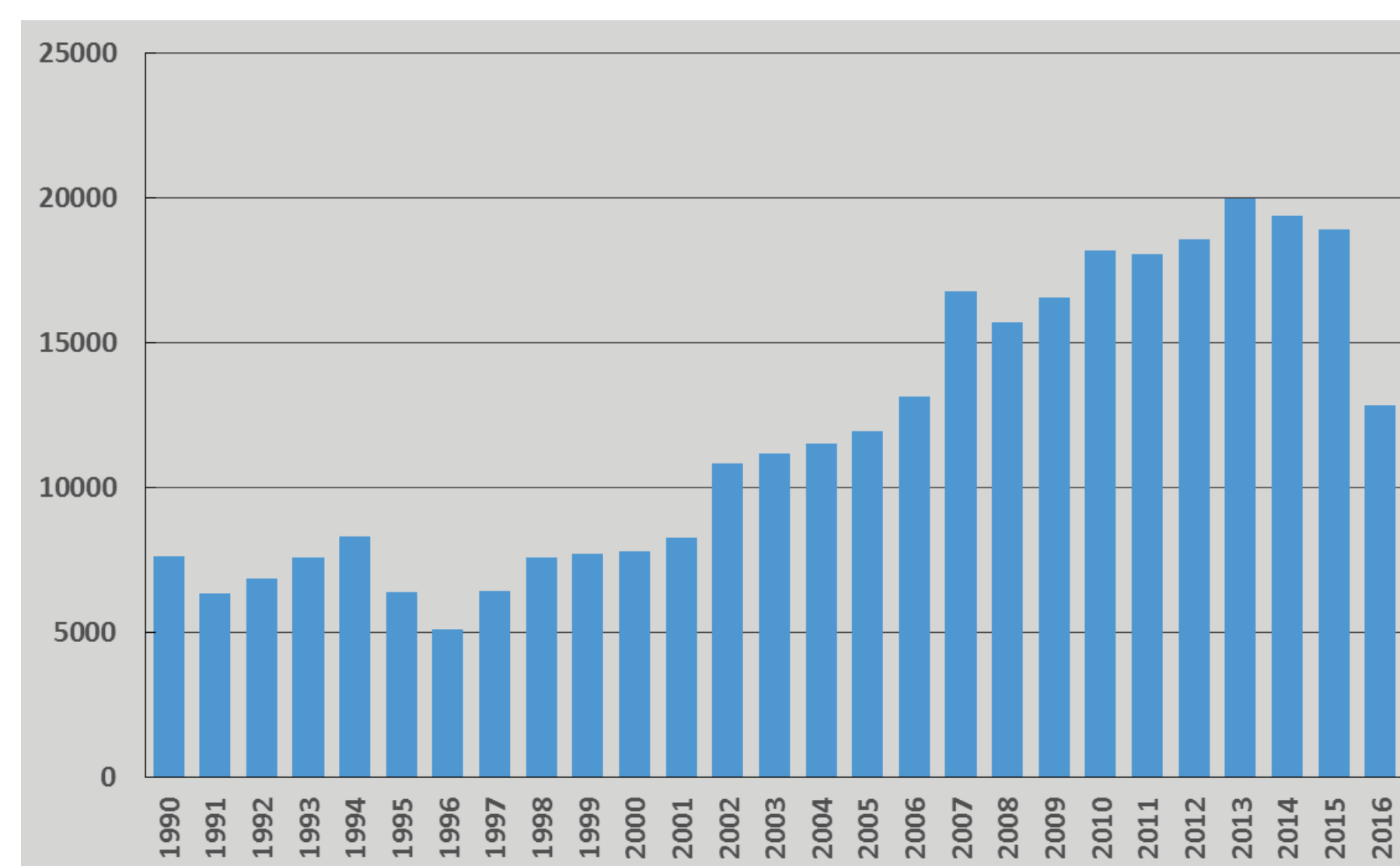


Figure 3: Number of case reports (all age groups) with suspected small molecule drugs 1990 to 2016 (approx. 320,000).

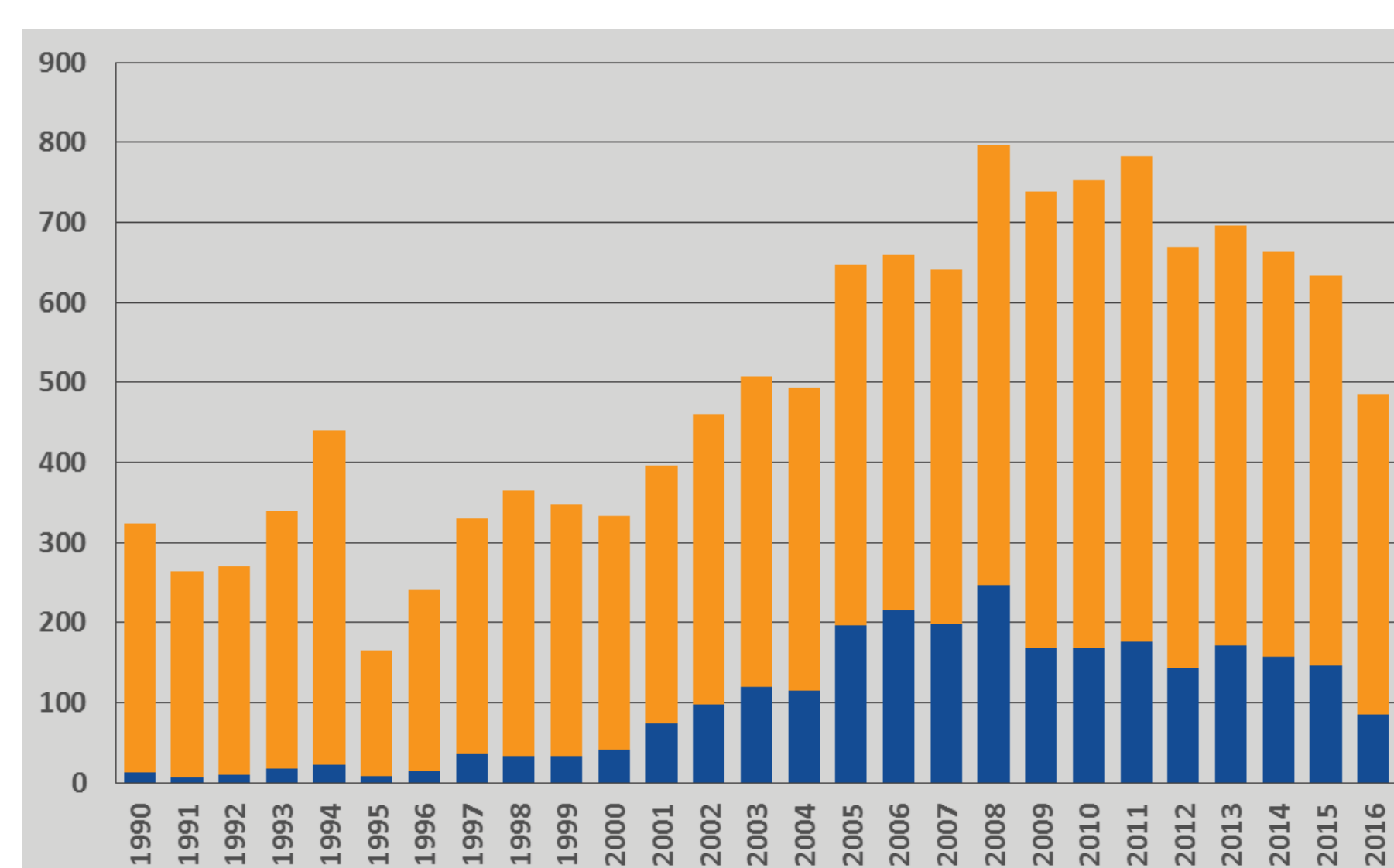


Figure 4: Number of case reports (age group 3–17 years) with suspected small molecule drugs 1990 to 2016 ( $n = 13,450$ ). Blue portion of columns: proportion of reports with suspected antipsychotics, antidepressants or stimulants.

Table 1: Ranking of the most frequently suspected substance in reports of adverse drug reactions associated with antipsychotics, antidepressants or stimulants.

Antipsychotics		Antidepressants		Stimulants	
Substance	No. of ICSRs	Substance	No. of ICSRs	Substance	No. of ICSRs
Risperidone	283	Fluoxetine	65	Methylphenidate	930
Clozapine	171	Citalopram	56	Atomoxetine	386
Aripiprazole	104	Venlafaxine	45	Lisdexamfetamine	92
Quetiapine	86	Escitalopram	34		
Olanzapine	96	Sertraline	35		
Chlorprothixene	77	Mirtazapine	32		
Pipamperone	82	Fluvoxamine	22		
Haloperidol	48	Agomelatine	15		

Table 2: The table conveys identified potential signals, defined as  $\geq 3$  reports of adverse reactions not labeled in the corresponding product information, and the results of a search for equivalent reports in PubMed and VigilLyze® (WHO database of spontaneous reports).

Substance	Potential signal (No. of reports)	Matching literature reports	Positive IC value in VigilLyze®
Methylphenidate	Priapism <sup>1</sup> (3)	+	+
	Qt-elongation (11)	+	+
	Speech disorder (10)	+	+
	Thrombocytosis (3)	+	+
Lisdexamfetamine	Obsessive-compulsive symptoms (7)	+	+
	Obsessive-compulsive symptoms <sup>2</sup> (3)	+	+

<sup>1</sup> signal verified by PRAC in December 2016

<sup>2</sup> labeled in the SPC of dexamfetamine (lisdexamfetamine acts as a prodrug to dexamfetamine)

## Conclusion

By using a basic methodology we revealed potential safety signals for the both substances with the highest number of records, methylphenidate and lisdexamfetamine. These signals should be further evaluated by other methods. The potential signal “obsessive-compulsive symptoms” found for lisdexamfetamine is already known for its active compound amphetamine. The revealed signal “priapism” for methylphenidate was recently verified by the Pharmacovigilance Risk Assessment Committee. Some of the most frequently suspected medicines in our analysis were used off-label in this age group.

## References:

- [1] Hawcutt D. et al. Reported paediatric adverse drug reactions in the UK 2000–2009. Br J Clin Pharmacol 2011; 73: 437–446.
- [2] <https://www.who-umc.org/vigibase/vigilyze/>
- [3] Zuddas A. et al. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: a review of the randomized controlled studies. Eur Neuropsychopharmacol 2011; 21: 600–620.

The authors have no conflict of interest directly relevant to the content of this poster presentation.